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Cubosomal Nanocarriers for Diabetic Wound Healing: Advances in Synthetic and Herbal Drug Delivery

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Abstract

Diabetic wounds remain one of the most challenging complications of diabetes mellitus, characterized by impaired angiogenesis, prolonged inflammation, microbial infection, and delayed tissue regeneration. Conventional therapies often fail to achieve effective drug penetration, sustained release, and targeted action at the wound site. In recent years, cubosomal nanocarriers have emerged as promising platforms for dermal and transdermal drug delivery, offering structural stability, high entrapment efficiency, and the ability to encapsulate both hydrophilic and lipophilic drugs. Their unique bicontinuous cubic phase architecture enhances skin permeation and provides controlled release, making them highly suitable for chronic wound management. This review highlights the advances in cubosome-based delivery of synthetic drugs (such as antidiabetic agents, antimicrobials, and growth modulators) and herbal actives (such as flavonoids, terpenoids, and polyphenols), with a focus on synergistic approaches that combine the pharmacological precision of synthetic drugs with the multi-targeted therapeutic benefits of phytoconstituents. We further discuss formulation strategies, characterization techniques, preclinical findings, and translational challenges that must be addressed to realize their clinical potential. Cubosomal nanocarriers thus represent a frontier in the design of multifunctional topical systems aimed at accelerating wound closure, minimizing infection, and restoring skin integrity in diabetic patients.

1.INTRODUCTION

Diabetes mellitus is a rapidly escalating global health problem, affecting over half a billion people worldwide and projected to increase dramatically in the coming decades (1, 2). Among its many complications, chronic wounds particularly diabetic foot ulcers (DFUs) are among the most debilitating, contributing to pain, infection, amputation, and mortality. These wounds are notoriously difficult to treat due to neuropathy, impaired blood flow, persistent infection, oxidative stress, and delayed tissue regeneration (3-5). Conventional topical therapies, such as ointments and creams, provide limited benefit in such complex wound environments because of poor skin penetration, rapid clearance, and inadequate bioavailability of active agents. This therapeutic gap has fueled interest in nanotechnology-based systems, which can enhance drug stability, prolong retention at the wound site, and promote controlled, localized release. Among lipid-based nanocarriers, cubosomes self-assembled, bicontinuous cubic-phase liquid crystalline nanoparticles have attracted significant attention. Their unique structure allows the encapsulation of both hydrophilic and lipophilic drugs, high bioadhesion, biocompatibility, and sustained delivery, making them well suited for chronic wound therapy (6-8). Recent advances highlight the potential of cubosomal gels as hybrid delivery platforms, capable of integrating synthetic drugs (e.g., antibiotics, insulin sensitizers, anti-inflammatories) with herbal phytoconstituents (e.g., curcumin, silymarin, neem, aloe vera) to achieve synergistic wound healing. Such combinations can simultaneously target multiple pathological mechanisms reducing infection, modulating inflammation, enhancing angiogenesis, and accelerating tissue repair (9, 10).

1.1 Global burden of diabetes and complications of chronic wounds.

Diabetes mellitus has reached epidemic proportions worldwide, with an estimated 537 million adults (20–79 years) living with the disease in 2021, a number projected to rise to 643 million by 2030 and 783 million by 2045 (International Diabetes Federation). Beyond its metabolic impact, diabetes is associated with debilitating complications, among which chronic wounds, especially diabetic foot ulcers (DFUs), represent a major clinical and socioeconomic burden (11-14).

- **Prevalence:** Approximately 15–25% of diabetic patients will develop a foot ulcer during their lifetime.
- **Amputations:** DFUs proceed up to 85% of lower-limb amputations in diabetic patients.
- **Mortality:** The 5-year mortality rate after a major amputation exceeds 50%, which is higher than many cancers.
- **Economic cost:** Global expenditure on diabetic foot complications is estimated in billions of US dollars annually, straining healthcare systems.

1.2 Why diabetic wounds are difficult to heal (neuropathy, poor circulation, infection, oxidative stress

Diabetic wounds, particularly foot ulcers, are characterized by delayed and impaired healing due to a complex interplay of pathological factors:

- **Peripheral neuropathy:** Loss of protective sensation leads to unnoticed trauma and repetitive pressure injuries. Autonomic neuropathy further reduces sweat and oil gland activity, causing dry, cracked skin that is more prone to ulceration.
- **Poor circulation:** Diabetes-induced microangiopathy and macroangiopathy reduce oxygen and nutrient delivery to tissues, impairing angiogenesis and collagen synthesis necessary for repair.
- **Infection susceptibility:** Hyperglycemia provides a favorable environment for microbial growth, while impaired immune cell function and persistent biofilm formation hinder infection control and prolong inflammation.
- **Oxidative stress and chronic inflammation:** Excessive generation of reactive oxygen species (ROS) damages cellular components, while persistent pro-inflammatory cytokine release delays granulation tissue formation and re-epithelialization (15, 16).

1.3 Need for advanced topical therapies over limitations of conventional creams/ointments

Topical therapy is the preferred route for treating diabetic wounds, as it allows localized drug delivery, reduces systemic side effects, and improves patient compliance (17). However, conventional formulations such as creams and ointments often fall short in managing the complex pathology of chronic wounds (18-20).

Limitations of conventional topical formulations:

- **Poor penetration:** Thickened skin and disrupted vasculature in diabetic wounds restrict drug permeation into deeper layers.
- **Rapid clearance:** Creams/ointments are easily removed by wound exudates, sweat, or dressing changes, leading to short drug residence time.
- **Uncontrolled release:** Conventional formulations cannot sustain drug levels, resulting in frequent reapplication and suboptimal therapeutic effects.
- **Drug instability:** Many synthetic drugs and herbal actives degrade rapidly when exposed to light, oxygen, or wound exudates.
- **Limited multifunctionality:** Most ointments address only one aspect (e.g., infection or moisture), whereas diabetic wounds require multi-targeted therapy (anti-infective, anti-inflammatory, angiogenic, antioxidant).

Given these challenges, there is a pressing need for advanced topical drug delivery systems that can:

- Enhance skin and tissue penetration.
- Provide sustained and controlled release of actives.
- Protect drugs from degradation in the wound microenvironment.
- Deliver combinational therapy by integrating both synthetic and herbal agents.
- Improve patient outcomes by accelerating wound closure and reducing recurrence.

2. DIABETIC WOUND PATHOPHYSIOLOGY

The pathophysiology of diabetic wounds is complex and multifactorial, involving a convergence of vascular, neural, immune, and biochemical abnormalities that together impair the normal wound-healing cascade (21-23). Unlike acute wounds, which follow a coordinated sequence of hemostasis, inflammation, proliferation, and remodeling, diabetic wounds are marked by prolonged inflammation, impaired angiogenesis, delayed granulation tissue formation, and incomplete re-epithelialization.

Key pathological mechanisms include:

- **Peripheral neuropathy:** Sensory neuropathy diminishes pain perception, leading to unnoticed injuries, while motor neuropathy alters foot biomechanics, causing pressure points and ulceration. Autonomic neuropathy further reduces sweating, leading to dry, fragile skin prone to cracking.
- **Vascular insufficiency:** Both microvascular (capillary basement membrane thickening, endothelial dysfunction) and macrovascular (atherosclerosis) complications reduce blood supply, oxygenation, and nutrient delivery, impairing tissue repair and angiogenesis.
- **Persistent infection:** Hyperglycemia compromises neutrophil chemotaxis and phagocytosis, lowering host defense. The warm, moist wound bed favors microbial colonization, while biofilm formation protects pathogens from antibiotics and immune responses, prolonging chronic infection.
- **Oxidative stress and inflammation:** Diabetes induces excessive generation of reactive oxygen species (ROS) and inflammatory cytokines (e.g., TNF-α, IL-6). These disrupt extracellular matrix remodeling, impair fibroblast and keratinocyte activity, and delay granulation tissue formation.
- **Impaired growth factor signaling:** Reduced expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF-1) limits angiogenesis, collagen deposition, and re-epithelialization.

2.1 Role of infection and biofilm in non-healing ulcers

Infection is one of the most critical barriers to wound healing in diabetic patients. Hyperglycemia creates a favorable environment for microbial growth, while impaired immune responses further compromise host defense. Neutrophil dysfunction, reduced chemotaxis, and impaired phagocytosis in diabetes limit the body’s ability to clear invading pathogens effectively. As a result, diabetic wounds are highly susceptible to colonization by polymicrobial communities, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and anaerobic bacteria. A major contributor to wound chronicity is the formation of biofilms structured microbial aggregates encased within a self-produced extracellular polymeric matrix (24-26).

Biofilms:

- Protect bacteria from antibiotics and host immune attack.
- Enhance horizontal gene transfer, contributing to antimicrobial resistance.
- Maintain a persistent inflammatory response, which damages surrounding tissues.

- Impede fibroblast migration and keratinocyte proliferation, thus delaying re-epithelialization.

2.2 Therapeutic targets that synthetic drugs and herbal actives can address (27, 28)

Effective management of diabetic wounds requires targeting multiple pathological mechanisms simultaneously. Both synthetic drugs and herbal actives offer distinct advantages by acting on complementary pathways involved in impaired wound healing:

A. Infection Control:

- **Synthetic drugs:** Antibiotics (e.g., gentamicin, mupirocin) inhibit bacterial growth and biofilm formation.
- **Herbal actives:** Plant-derived antimicrobials (e.g., neem, curcumin, aloe vera) possess broad-spectrum antibacterial, antifungal, and anti-biofilm properties.

B. Inflammation Modulation:

- **Synthetic drugs:** Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid derivatives reduce excessive cytokine release and inflammation.
- **Herbal actives:** Flavonoids (e.g., silymarin, quercetin) and polyphenols exhibit antioxidant and anti-inflammatory activity, scavenging reactive oxygen species (ROS) and modulating NF-κB signaling.

C. Angiogenesis and Tissue Regeneration:

- **Synthetic drugs:** Growth factor mimetics (VEGF, PDGF) or insulin sensitizers enhance endothelial proliferation, collagen deposition, and granulation tissue formation.
- **Herbal actives:** Asiaticoside, curcumin, and aloe vera promote fibroblast proliferation, collagen synthesis, and neovascularization.

D. Oxidative Stress Reduction:

- **Synthetic drugs:** Antioxidants like N-acetylcysteine help neutralize ROS.
- **Herbal actives:** Polyphenols and flavonoids reduce oxidative damage, restoring cellular function in keratinocytes and fibroblasts.

E. Moisture Balance and Extracellular Matrix Support:

- **Synthetic drugs:** Hydrogel-forming polymers and collagen analogs maintain a moist environment and support ECM deposition.
- **Herbal actives:** Aloe vera and other mucilaginous extracts provide hydration and stimulate ECM remodeling.

3. NANOTECHNOLOGY IN WOUND HEALING

The complexity of diabetic wounds marked by infection, oxidative stress, impaired angiogenesis, and chronic inflammation has driven the search for advanced therapeutic strategies beyond conventional topical formulations (29-31). Nanotechnology-based drug delivery systems have emerged as promising tools due to their ability to enhance targeted delivery, bioavailability, and controlled release of therapeutic agents at the wound site.

Key advantages of nanocarriers in wound healing include:

- **Improved penetration:** Nanoparticles can traverse the skin barrier and infiltrate deeper layers, ensuring effective drug delivery to the wound microenvironment.
- **Sustained and controlled release:** Nanocarriers allow gradual release of active compounds, maintaining therapeutic concentrations over prolonged periods and reducing the frequency of application.
- **Protection of actives:** Encapsulation shields sensitive drugs and herbal actives from enzymatic degradation, oxidation, and hydrolysis in the wound bed.
- **Multifunctionality:** Nanocarriers can co-deliver multiple agents, such as antibiotics with anti-inflammatory or angiogenic compounds, achieving synergistic therapeutic effects.
- **Enhanced wound healing outcomes:** Nanocarrier systems can promote angiogenesis, collagen deposition, re-epithelialization, and reduced microbial load more effectively than conventional creams (31-34).

Common types of nanocarriers used in wound healing:

1. **Lipid-based carriers:** Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) provide biocompatibility and high drug-loading capacity (35).
2. **Polymeric nanoparticles:** Biodegradable polymers such as PLGA and chitosan enhance sustained drug release and antimicrobial activity (36).
3. **Metallic nanoparticles:** Silver and gold nanoparticles possess inherent antimicrobial and anti-inflammatory properties (37).
4. **Cubosomes:** Bicontinuous cubic-phase nanoparticles that combine high surface area, encapsulation of hydrophilic and lipophilic drugs, and bioadhesion, making them ideal for diabetic wound therapy (38).

3.1 Why nanocarriers are attractive: penetration, sustained release, bioadhesion, infection control

Nanocarriers offer several unique advantages that make them particularly suited for diabetic wound management, addressing the limitations of conventional therapies:

1. **Enhanced Penetration:**
   - Nanoparticles can penetrate the stratum corneum and reach deeper layers of the skin and wound bed.
   - This ensures that therapeutic agents, whether synthetic drugs or herbal actives, reach the target site in effective concentrations (39, 40).
2. **Sustained and Controlled Release:**
   - Nanocarriers can provide gradual release of encapsulated drugs over extended periods.
   - This minimizes the need for frequent applications and maintains therapeutic levels at the wound site, improving patient compliance (41-43).
3. **Bioadhesion:**
   - Many nanocarriers, such as cubosomes or polymeric nanoparticles, exhibit strong adhesion to wound surfaces, prolonging residence time.
   - This ensures localized delivery and reduces drug loss due to wound exudate or dressing changes (44).
4. **Infection Control:**

- Nanocarriers can enhance the delivery of antimicrobial agents directly into biofilms and infected tissue.
- Some nanomaterials (e.g., silver nanoparticles, chitosan-based carriers) possess intrinsic antimicrobial activity, helping reduce bacterial load and support wound healing (45, 46).

3.2 Short overview of lipid-based nanocarriers (niosomes, liposomes, solid lipid nanoparticles, cubosomes)

Lipid-based nanocarriers have gained significant attention in wound healing due to their biocompatibility, ability to encapsulate diverse drugs, and controlled release properties. These systems can improve drug penetration, protect sensitive actives, and enhance therapeutic efficacy (47-49).

1. Niosomes:

- Non-ionic surfactant vesicles that can encapsulate both hydrophilic and lipophilic drugs.
- Advantages: low toxicity, improved stability over liposomes, and enhanced skin penetration (50).

2. Liposomes:

- Phospholipid bilayer vesicles resembling cell membranes.
- Advantages: biocompatible, versatile in drug loading, capable of sustained release, but sometimes limited by stability and rapid clearance (51).

3. Solid Lipid Nanoparticles (SLNs):

- Composed of solid lipids stabilized by surfactants.
- Advantages: high stability, controlled drug release, protection of labile compounds, and good skin adhesion (52).

4. Cubosomes:

- Bicontinuous cubic-phase lipid nanoparticles with high internal surface area.
- Advantages: can encapsulate both hydrophilic and lipophilic actives, bioadhesive, controlled release, and ideal for co-delivery of synthetic and herbal drugs in diabetic wounds (53-55).

3.3 Distinction of cubosomes vs. others (56-60)

While several lipid-based nanocarriers are employed in wound healing, cubosomes offer unique structural and functional advantages that distinguish them from niosomes, liposomes, and solid lipid nanoparticles (SLNs):

Feature	Niosomes	Liposomes	SLNs	Cubosomes
Structure	Non-ionic surfactant bilayer vesicles	Phospholipid bilayer vesicles	Solid lipid matrix	Bicontinuous cubic-phase lipid nanoparticles
Drug Loading	Hydrophilic & lipophilic	Hydrophilic & lipophilic	Primarily lipophilic	Hydrophilic & lipophilic; high capacity due to cubic structure
Stability	Moderate	Moderate; prone to leakage	High	Very high; resistant to degradation and aggregation
Controlled Release	Moderate	Moderate	Good	Excellent; sustained release over long periods
Bioadhesion	Moderate	Low-moderate	Good	High; adheres well to wound surfaces
Multidrug Co-delivery	Limited	Limited	Moderate	Excellent; can deliver multiple synthetic and herbal actives simultaneously
Suitability for Chronic Wounds	Good	Good	Good	Superior; ideal for diabetic wound healing due to penetration, sustained release, and multifunctionality

4. Cubosomal Nanocarriers: Properties and Mechanisms

Cubosomes are nanostructured lipid-based carriers with a bicontinuous cubic-phase internal architecture, composed of amphiphilic lipids (e.g., glycerol monooleate) stabilized by surfactants (e.g., poloxamer 407). Their unique structure provides distinct physicochemical and biological properties that make them ideal for diabetic wound healing applications (61, 62).

4.1 Key Properties of Cubosomes (63-65)

1. **High Drug Loading Capacity:**
   - The internal cubic network allows encapsulation of both hydrophilic and lipophilic drugs simultaneously.
2. **Biocompatibility and Biodegradability:**
   - Made from lipids similar to biological membranes, cubosomes are generally well-tolerated and biodegradable.
3. **Controlled and Sustained Release:**
   - The tortuous water channels provide prolonged release of therapeutic agents, reducing application frequency.
4. **Bioadhesion:**
   - Cubosomes can adhere to wound surfaces, enhancing localized delivery and minimizing drug loss due to exudates.
5. **Stability:**
   - Resistant to aggregation and degradation compared to conventional lipid vesicles, ensuring prolonged shelf life.

4.2 Mechanisms of Action in Wound Healing (66-70)

1. **Enhanced Penetration:**

- ○ Nanometer-sized cubosomes facilitate deep penetration into the wound bed, ensuring effective drug delivery.

2. **Infection Control:**
   - ○ Deliver antimicrobial agents directly to biofilm-embedded bacteria, improving bacterial clearance.
3. **Inflammation Modulation:**
   - ○ Co-delivery of anti-inflammatory or antioxidant agents reduces excessive ROS and cytokine activity, supporting tissue repair.
4. **Promotion of Angiogenesis and Tissue Regeneration:**
   - ○ Encapsulated growth factors, synthetic drugs, or herbal actives stimulate fibroblast proliferation, collagen deposition, and neovascularization, accelerating wound closure.
5. **Synergistic Co-Delivery:**
   - ○ Cubosomes can simultaneously carry synthetic drugs and herbal phytoconstituents, enabling multi-targeted therapy in diabetic wounds.

4.3 Structural features: bicontinuous cubic phase, high surface area, and biocompatibility

Cubosomes are nanostructured lipid particles characterized by a bicontinuous cubic-phase internal structure, which distinguishes them from other lipid-based carriers. Their key structural features include:

1. **Bicontinuous Cubic Phase:**
   - ○ The lipid matrix forms a three-dimensional, interconnected network of aqueous channels.
   - ○ This allows simultaneous encapsulation of hydrophilic and lipophilic drugs, making cubosomes highly versatile (71, 72).
2. **High Surface Area:**
   - ○ The intricate cubic architecture provides an extensive internal surface area, enhancing drug loading capacity and interaction with wound tissues (73, 74).
3. **Biocompatibility:**
   - ○ Composed of lipids similar to biological membranes (e.g., glycerol monooleate) and stabilized by biocompatible surfactants, cubosomes are generally non-toxic and biodegradable, minimizing adverse reactions (75, 76).

These structural attributes underpin the controlled release, bioadhesion, and multifunctionality of cubosomes, making them an ideal platform for localized, sustained, and synergistic drug delivery in diabetic wound healing (77).

4.4 Advantages of Cubosomes (78-80)

Cubosomes offer several advantages over conventional lipid-based carriers, making them highly suitable for diabetic wound therapy:

1. **High Stability:**
   - ○ Cubosomes are resistant to aggregation and degradation, ensuring longer shelf life and consistent therapeutic performance.
2. **Versatile Drug Encapsulation:**
   - ○ The bicontinuous cubic structure allows simultaneous loading of hydrophilic and lipophilic drugs, including both synthetic and herbal actives.
3. **Controlled and Sustained Release:**
   - ○ The intricate internal network provides prolonged and regulated drug release, maintaining therapeutic concentrations at the wound site and reducing the frequency of application.
4. **Bioadhesion:**
   - ○ Cubosomes can adhere to wound surfaces, improving localized drug delivery and minimizing drug loss due to exudates.
5. **Multifunctional Therapy:**
   - ○ Ability to co-deliver antimicrobials, anti-inflammatory agents, growth factors, and herbal extracts, enabling synergistic wound healing

4.5 Preparation Methods of Cubosomes (81-84)

Cubosomes can be prepared using two main strategies: **top-down** and **bottom-up**, each with distinct advantages and considerations for drug delivery applications.

1. Top-Down Method

- **Principle:** Bulk cubic-phase lipid is first formed and then dispersed into nanoscale particles using high-energy techniques.
- **Process:**
  1. Lipid (e.g., glycerol monooleate) and surfactant (e.g., poloxamer 407) are mixed and heated to form a viscous bulk cubic phase.
  2. The bulk phase is sheared using high-pressure homogenization or ultrasonication to generate nanosized cubosomes.
- **Advantages:**
  - ○ Produces uniform particle size and high structural stability.
  - ○ Suitable for encapsulating both hydrophilic and lipophilic drugs.

Limitations:

- ○ Requires specialized equipment and high energy input.
- ○ Heat-sensitive drugs may degrade during processing.

2. Bottom-Up Method

- **Principle:** Cubosomes are formed spontaneously from lipid molecules in solution, often using solvent dilution or nanoprecipitation.
- **Process:**
  1. Lipid is dissolved in a water-miscible solvent.
  2. The solution is added to an aqueous surfactant solution, causing self-assembly into cubosomes.
- **Advantages:**
  - ○ Gentle process suitable for thermo-sensitive drugs (e.g., proteins, herbal extracts).
  - ○ Energy-efficient and simple to scale up.

Limitations:

  - May result in heterogeneous particle size, requiring post-processing.

5. Synthetic Drugs in Cubosomal Delivery for Diabetic Wounds (85-87)

Synthetic drugs play a critical role in targeting the multifactorial pathology of diabetic wounds, including infection, inflammation, oxidative stress, and impaired tissue regeneration. Encapsulating these drugs in cubosomal nanocarriers enhances their stability, bioavailability, and localized therapeutic effects, making them more effective than conventional topical formulations.

5.1 Common Synthetic Drugs Used (88-91)

1. **Antibiotics** (e.g., gentamicin, mupirocin, vancomycin)
   - Target bacterial infections and disrupt biofilms.
   - Cubosomal encapsulation improves penetration into wound tissues and biofilms.
2. **Anti-inflammatory Agents** (e.g., NSAIDs, corticosteroid derivatives)
   - Reduce chronic inflammation by modulating pro-inflammatory cytokines such as TNF-α and IL-6.
   - Sustained release from cubosomes maintains local anti-inflammatory effects.
3. **Growth Factor Mimetics and Tissue Regenerators** (e.g., PDGF, VEGF analogs, insulin sensitizers like glibenclamide)
   - Promote angiogenesis, fibroblast proliferation, collagen deposition, and granulation tissue formation.
   - Cubosomes protect sensitive growth factors from degradation in the wound microenvironment.
4. **Antioxidants** (e.g., N-acetylcysteine, ascorbic acid derivatives)
   - Reduce oxidative stress and ROS-mediated cellular damage.
   - Controlled release ensures prolonged antioxidant activity.

5.2 Advantages of Cubosomal Delivery for Synthetic Drugs

- **Enhanced stability:** Protects labile drugs from enzymatic degradation and oxidation.
- **Controlled release:** Maintains therapeutic concentrations at the wound site over extended periods.
- **Targeted delivery:** Bioadhesive properties ensure drugs remain localized, minimizing systemic exposure.
- **Synergistic potential:** Can be co-formulated with herbal actives for multi-targeted therapy.

5.3 Example Studies

- Glibenclamide-loaded cubosomal gels showed improved diabetic wound closure in preclinical models by promoting angiogenesis and modulating inflammatory markers.
- Antibiotic-loaded cubosomes enhanced penetration into biofilm-laden wounds, leading to faster microbial clearance compared to conventional ointments.

5.4 Mechanism of action in wound healing (92, 93)

When synthetic drugs are delivered via cubosomal nanocarriers, they act through multiple mechanisms to promote diabetic wound healing:

1. **Infection Control:**
   - Antibiotics encapsulated in cubosomes penetrate biofilms and infected tissue, inhibiting bacterial growth and preventing further microbial colonization.
   - Reduced bacterial load decreases prolonged inflammation and tissue damage.
2. **Inflammation Modulation:**
   - Anti-inflammatory drugs reduce overproduction of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.
   - This attenuates chronic inflammation, allowing fibroblasts and keratinocytes to migrate and proliferate.
3. **Promotion of Angiogenesis and Tissue Regeneration:**
   - Growth factor mimetics or insulin sensitizers enhance endothelial cell proliferation, collagen deposition, and granulation tissue formation.
   - Cubosomal delivery protects these sensitive molecules from degradation and ensures localized, sustained release at the wound site.
4. **Oxidative Stress Reduction:**
   - Encapsulated antioxidants neutralize reactive oxygen species (ROS), preventing cellular and extracellular matrix damage.
   - This supports keratinocyte and fibroblast function, accelerating re-epithelialization.
5. **Synergistic Effects:**
   - Cubosomes allow co-delivery of multiple synthetic drugs or synthetic–herbal combinations, targeting infection, inflammation, oxidative stress, and angiogenesis simultaneously.
   - This multi-targeted approach addresses the multifactorial nature of diabetic wounds more effectively than single-drug therapies.

6. Herbal/Phytoconstituents in Cubosomes

Herbal and plant-derived actives (phytoconstituents) have been extensively investigated for diabetic wound healing due to their antioxidant, anti-inflammatory, antimicrobial, and tissue-regenerative properties. Encapsulation in cubosomal nanocarriers enhances their stability, bioavailability, and localized delivery, making them more effective than conventional formulations (94).

6.1 Common Herbal Actives Used (95-98)

1. **Curcumin (from turmeric):**
   - Potent antioxidant and anti-inflammatory agent.
   - Promotes fibroblast proliferation, collagen synthesis, and angiogenesis.
2. **Silymarin (from milk thistle):**
   - Reduces oxidative stress and inflammation.
   - Stimulates granulation tissue formation and re-epithelialization.
3. **Neem (Azadirachta indica) extracts:**
   - Broad-spectrum antimicrobial activity.
   - Enhances wound contraction and tissue repair.

4. **Aloe vera:**
    - Moisturizes and protects wound bed.
    - Promotes collagen deposition and epithelialization.
5. **Asiaticoside (from Centella asiatica):**
    - Stimulates fibroblast activity, collagen synthesis, and angiogenesis.

6.2 Advantages of Cubosomal Delivery for Herbal Actives (99)

- **Enhanced stability:** Protects sensitive phytoconstituents from oxidation and degradation.
- **Improved penetration:** Nanocarriers facilitate deeper tissue delivery.
- **Controlled release:** Maintains effective concentrations over time, reducing frequent application.
- **Synergistic potential:** Co-delivery with synthetic drugs enables multi-targeted therapy addressing infection, inflammation, oxidative stress, and tissue regeneration.

6.3 Example Studies (100, 101)

- Curcumin-loaded cubosomal gels showed accelerated wound closure and reduced inflammation in diabetic wound models.
- Silymarin encapsulated in cubosomes enhanced angiogenesis and granulation tissue formation, outperforming conventional topical formulations.

6.4 Advantages of herbal actives (102-104)

Herbal or plant-derived actives (phytoconstituents) offer several benefits when delivered via cubosomal nanocarriers for diabetic wound healing:

1. **Multifunctional Therapeutic Effects:**
    - Possess antioxidant, anti-inflammatory, antimicrobial, and angiogenic properties, addressing multiple aspects of diabetic wound pathology simultaneously.
2. **Synergistic Potential:**
    - Can be co-delivered with synthetic drugs in cubosomes, enhancing therapeutic efficacy through multi-targeted action.
3. **Biocompatibility and Safety:**
    - Generally non-toxic, biodegradable, and well-tolerated, reducing the risk of side effects compared to synthetic drugs.
4. **Enhanced Stability:**
    - Encapsulation in cubosomes protects sensitive phytoconstituents from degradation caused by light, oxidation, or enzymes in the wound microenvironment.
5. **Controlled and Sustained Release:**
    - The cubic nanostructure allows gradual release of herbal actives, maintaining therapeutic concentrations at the wound site and reducing application frequency.
6. **Improved Penetration:**
    - Nanocarrier size and bioadhesive properties facilitate deeper penetration into wound tissue, enhancing efficacy in chronic wounds.

6.5 Synergistic Delivery of Synthetic and Herbal Actives in Cubosomes

Chronic diabetic wounds involve multifactorial pathophysiology, including infection, inflammation, oxidative stress, and impaired tissue regeneration. Single-agent therapies often fail to address all these mechanisms effectively. Cubosomal nanocarriers provide a unique platform for co-delivery of synthetic drugs and herbal/phytoconstituents, enabling synergistic therapeutic effects (105-107).

Mechanisms of Synergy (108, 109)

1. **Multi-Targeted Action:**
    - Synthetic drugs (e.g., antibiotics, anti-inflammatory agents) control infection and inflammation.
    - Herbal actives (e.g., curcumin, silymarin, aloe vera) provide antioxidant activity, promote angiogenesis, and accelerate tissue repair.
    - Co-delivery targets multiple wound-healing pathways simultaneously, enhancing overall efficacy.
2. **Enhanced Drug Stability and Bioavailability:**
    - Cubosomal encapsulation protects both synthetic and herbal actives from degradation and premature clearance, maintaining effective concentrations at the wound site.
3. **Controlled and Sustained Release:**
    - The cubic nanostructure allows synchronized release of multiple agents over time, ensuring prolonged therapeutic activity and reducing the frequency of application.
4. **Improved Penetration and Bioadhesion:**
    - Nanocarrier size and bioadhesive properties facilitate deep tissue delivery, ensuring that all co-encapsulated actives reach the target site effectively.

7. Current Research Advances in Cubosomal Delivery for Diabetic Wound Healing

Recent studies have highlighted the potential of cubosomal nanocarriers in enhancing the efficacy of diabetic wound healing therapies. Key advancements include:

7.1 Enhanced Drug Delivery Systems

- **Simvastatin-Loaded Cubosomes**: A study demonstrated that simvastatin-loaded cubosomal gels (cubogels) significantly accelerated wound healing in diabetic rats compared to conventional treatments. The cubogels provided sustained drug release, improved skin permeation, and enhanced wound closure rates (110).
- **Hesperidin-Loaded Cubogels**: Research on hesperidin-loaded cubogels indicated that this formulation effectively mitigated full-thickness wounds. The cubogel system enhanced the stability and bioavailability of hesperidin, promoting wound healing processes (111).

7.2 Co-Delivery of Synthetic and Herbal Actives

- **Simvastatin and Herbal Combinations**: Investigations into the co-delivery of simvastatin with herbal extracts in cubosomal formulations have shown synergistic effects in diabetic wound healing. These combinations address multiple aspects of wound pathology, including inflammation and tissue regeneration (112).

7.3 Advanced Hydrogel Formulations

- **Cubosome-Based Hydrogels**: The development of cubosome-based hydrogels has provided a promising platform for intelligent medication delivery. These hydrogels offer controlled drug release, enhanced tissue penetration, and improved therapeutic outcomes in wound healing (113).

7.4 Innovative Drug Delivery Strategies

- **N-Alkylated Benzimidazole Cubosomes:** A novel approach involving N-alkylated benzimidazole-based cubosome hydrogels has been explored for the topical treatment of burns. This formulation demonstrated effective drug release and promoted wound healing in preclinical models (114).

7.5 Comparative Outcomes of Cubosomal Formulations (115-117)

Recent studies evaluating cubosome-based drug delivery systems for diabetic wound healing have demonstrated superior outcomes compared to conventional formulations:

1. **Faster Wound Closure:**
   - ○ Cubosomal gels and hydrogels significantly accelerate wound contraction and epithelialization.
   - ○ Sustained release and deep tissue penetration of active agents ensure continuous therapeutic activity, reducing healing time.
2. **Higher Tensile Strength:**
   - ○ Treated wounds show improved collagen deposition and tissue remodeling, resulting in stronger, more resilient healed skin.
   - ○ Co-delivery of growth-promoting synthetic drugs and herbal actives enhances fibroblast proliferation and extracellular matrix formation.
3. **Reduced Infection Load:**
   - ○ Encapsulation of antibiotics and antimicrobial herbal extracts in cubosomes improves penetration into biofilms and infected tissue.
   - ○ This leads to a significant reduction in bacterial burden, lowering the risk of chronic infection and recurrence.

7.6 Cubosomal Formulations for Diabetic Wound Healing

Study	Active Ingredient	Polymer/Surfactant	Preparation Method	Key Outcomes
Simvastatin Cubosomal Nanoparticles	Simvastatin	Glyceryl Monooleate (GMO), Poloxamer 407	Top-down homogenization	Enhanced skin permeation, sustained release, and improved wound healing in rats (110).
Localized Delivery of Roxadustat via Cubosomes-Based Thermosensitive In-Situ Hydrogel	Roxadustat	Not specified	Thermosensitive hydrogel incorporation	Potentiated HIF-1α stabilization, enhanced angiogenesis, and accelerated wound healing in diabetic rats (118).
Accelerative Effect of Carbazole Nanocubosomes on the Healing of Diabetic Wounds	Carbazole	Not specified	Not specified	Significant reduction in bacterial counts, accelerated wound healing in diabetic rats (119).
Development of N-Alkylated Benzimidazole Based Cubosome Hydrogel for Burn Wounds	N-Alkylated Benzimidazole Derivative	Glyceryl Monooleate (GMO), Poloxamer 407	Homogenization method	Enhanced drug release, improved wound healing in burn models (120).

8. CHALLENGES AND LIMITATIONS

Developing synthetic–herbal topical formulations presents several challenges. One of the foremost is formulation complexity, where achieving optimal stability, entrapment efficiency, and sustained release for both types of actives can be difficult. Herbal variability further complicates this process, as batch-to-batch differences in phytoconstituents such as neem or silymarin often affect reproducibility (121). Another challenge lies in drug-drug interactions, since combining synthetic and herbal drugs may lead to antagonistic or unpredictable effects. Skin barriers add to the difficulty, with the stratum corneum limiting penetration while creating the risk of unintended systemic absorption (122). Analytical hurdles also exist, as simultaneous estimation and quantification of both actives using standard methods can be technically demanding. Finally, regulatory gaps pose a significant challenge, since clear guidelines for herbal–synthetic combinations are still lacking, making approval processes more complex. Despite encouraging progress, these systems carry certain limitations. A key concern is the in-vitro versus in-vivo gap, where promising laboratory results may not fully translate into human wound or skin healing outcomes (123). Animal models, while widely used, often fail to capture the full complexity of human diabetic wounds or infections. Short-term preclinical studies also provide limited insights, as chronic conditions typically persist for far longer durations. Safety concerns must be acknowledged as well, since long-term risks of irritation, sensitization, or allergenicity from herbal actives are not always fully explored (124). Finally, scalability remains a limitation; methods that work well at laboratory scale, such as cubosome or in-situ gel preparation, may not directly adapt to industrial manufacturing processes without significant modification (125, 126).

9. FUTURE PERSPECTIVES

Future research on synthetic-herbal topical formulations holds significant promise for improving wound healing and antifungal therapy. Advances in nanotechnology, such as cubosomes and other lipid-based carriers, can be further optimized to enhance drug penetration, stability, and targeted delivery while minimizing systemic absorption. Standardization of herbal extracts, through advanced analytical tools and fingerprinting techniques, will help overcome the issue of phytochemical variability and ensure reproducibility across batches. Multi-drug delivery systems can be fine-tuned to harness true synergistic effects between synthetic and herbal actives, supported by robust mechanistic studies at molecular and cellular levels. In the translational context, more predictive models such as 3D human skin equivalents or bioengineered diabetic wound models are expected to bridge the gap between preclinical studies and real-world outcomes. Long-term safety evaluations and controlled clinical trials will be essential to establish both efficacy and tolerability in patients. From a regulatory standpoint, clearer frameworks for herbal-synthetic combinations may emerge, streamlining the path to approval. Finally, efforts in green chemistry and scalable manufacturing could make these innovative formulations not only effective but also sustainable and commercially viable.

2. CONSLUSION

The development of synthetic-herbal topical formulations offers a promising strategy for addressing complex conditions such as chronic wounds and fungal infections. By combining the precision of synthetic drugs with the broad-spectrum bioactivity of herbal actives, these systems can potentially achieve synergistic effects, enhanced dermal penetration, and sustained therapeutic action. However, challenges related to formulation complexity, variability of herbal constituents, and regulatory uncertainties remain significant hurdles. Limitations in current experimental models and scalability further highlight the need for careful translation from laboratory to clinical settings. Despite these barriers, the field continues to advance through innovations in nanocarrier design, analytical standardization, and translational research. With sustained efforts toward optimizing stability, safety, and large-scale feasibility, synthetic-herbal drug delivery systems hold strong potential to emerge as next-generation therapeutics in wound management and antifungal therapy.

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